REMARKS/ARGUMENTS

Reconsideration of this application is requested.

Amendments to the Claims

The following amendments have been made to the claims:

1. Claim 61 is amended to be dependent on claim 60.

2. Claims 51 and 52 are amended to be dependent on claims 49 and 48, respectively.

2. Claims 48 and 49 are amended to specify that C_{ther} is 0.8 to 2 ng/ml, based on page 18, lines 3 and 4 of the application as originally filed. T_{maint} is also to be amended back to at least 2 hours, based on page 18, line 5.

2. In claims 51 and 52, T_{maint} is amended to 2 to 4 hours. Basis for this is provided by page 18, line 7.

2. New claims 67 to 69 are introduced. These are based on current claims 48 to 50 and specify that a therapeutic plasma concentration of 0.4 to 5 ng/ml is produced within 2 to 15 minutes and is maintained for a duration of from 2 to 4 hours. Basis for these claims is provided by page 18, lines 8 to 10 combined with page 18, line 3.

The new and amended claims find basis in the original description as explained above and do not introduce added subject matter.

Summary of the Present Invention

The present invention sets out to provide nasal buprenorphine compositions for systemic action with

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained,

resulting in the major advantage when used in the treatment of pain of

i) relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia **and**

iii) analgesia that is well sustained.

One of the ways in which this profile is achieved is to provide a liquid which is sufficiently fluid to be readily sprayed into the nose, but is sufficiently viscous and/or gels on the mucosa to hold the drug *in situ*.

Turning now to the points of the action in order:

Claim objections

The dependency of claim 61 has been amended.

Claim rejections - 35 USC 112

Claims 51 and 52 have been amended to be dependent on claims of the appropriate category.

Claims 48 to 52

Claims 48 to 52 were rejected for failing to comply with the written description requirement. An objection was also raised that there was no support in the specification for the previously presented limitations to the pharmacokinetic profile. However, the current version of the claims clearly fulfils these requirements.

Claims 48 and 49 relate to a buprenorphine composition and method of treatment defined by the plasma concentration-time profile obtained on administration. Both independent claims require that within 0.5 to 20 minutes a therapeutic plasma concentration of 0.8 to 2 ng/ml is reached which is maintained for at least 2 hours.

Such requirements are not fulfilled by the compositions of Eriksen. According to Table 3 of Eriksen, by 120 minutes the concentration of buprenorphine is 0.62 ng/ml. In contrast in claims 48 and 49 the concentration at this time has to be from 0.8 to 2ng/ml.

The subject matter of these claims is thus novel over the formulations of Eriksen.

Although no S103 rejection of claims 48 to 50 has been made, it is commented on here for completeness. Eriksen fails to disclose the present buprenorphine formulations, since its resultant plasma level fall below 0.8 ng/ml after 2 hr.

Eriksen is thus not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides

i) relatively rapid onset of analgesia after administration,

ii) a close to optimum level of analgesia **and**

iii) analgesia that is well sustained.

Even if Eriksen were considered, it nowhere teaches to adjust its formulations to achieve the major advantages of

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained at a level of 0.8 to 2ng/ml after at least 2 hr.

The subject matter of these claims is thus not only novel over the formulations of Eriksen, but Eriksen does not render these claims obvious.

Claims 67 to 69

These new claims relate to the intranasal administration buprenorphine wherein a therapeutic plasma concentration of 0.4 to 5 ng/ml is produced within 2 to 15 minutes which is maintained for a duration of from 2 to 4 hours. Thus similar to claims 48 to 52 above, these claims are also concerned with the provision of a composition which provides

i) relatively rapid onset of analgesia after administration,

ii) a close to optimum level of analgesia **and**

iii) analgesia that is well sustained.

In Eriksen, the mean plasma concentration after 4 hours is 0.34 ng/ml. In contrast, claims 67 to 69 have a lower limit of 0.4 ng/ml for the period of 2 to 4 hours. The present claims are thus novel over Eriksen.

In addition, claims 67 to 69 are also not obvious from Eriksen for the reasons given above for claims 48 to 52, *i.e.* Eriksen is not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides

i) relatively rapid onset of analgesia after administration,

ii) a close to optimum level of analgesia **and**

iii) analgesia that is well sustained.

Even if Eriksen were considered, it nowhere teaches to adjust its formulations to achieve the major advantages of

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained at a level of 0.4 to 5 ng/ml for from 2 to 4 hours.

Claims 67 to 69 are thus novel over the formulations of Eriksen, and Eriksen also does not render these claims obvious.

Claims 1 -15, 38, 39, 41

A §103 rejection of claims 1 - 15, etc has been made over Eriksen as the primary citation viso Watts, Reich and Nairn.

Eriksen, as indicated in its title, is concerned with the systematic availability of buprenorphine by nasal spray. In the introduction to this document, it is explained how sublingual administration of buprenorphine, although convenient, can be inappropriate for severely acutely presenting pain due to the slow speed of delivery. The authors of Eriksen therefore investigated whether intranasal delivery would provide an improvement in the speed of delivery.

Watts, on the other hand, is directed towards a completely different goal. Whereas Eriksen is concerned with increasing the speed of delivery of a drug, Watts is directed towards "control[ling] the plasma level *versus* time profile for readily absorbable drugs which are intended to act systematically (i.e. to give a flatter profile)" (page 14, lines 13 to 15). In light of the fact that the objectives of the two documents are completely different, the skilled person would not consider their teaching would be in any way compatible.

The present invention is concerned with the provision of buprenorphine compositions which provide

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained.

In Watts, in relation to systematically acting drugs, the aim is to provide a flatter profile for their administration. This is clearly illustrated in the figure which appears on the front page of this document in which the pectin containing fexofenadine has a completely flat release profile. Based on this, there is no way that the skilled person would consider the teaching of Watts when looking to provide compositions which have a relatively high maximum plasma concentration at a relatively short time after administration. In fact Watts teaches completely away from such effects since it is for example concerned with "retarding absorption of readily absorbable drugs" (page 14, lines 16 and 17).

Thus the combination of Erikson and Watts is not one that would be considered by the skilled person when seeking to provide buprenorphine compositions for systemic action which produce

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained,

resulting in the major advantage when used in the treatment of pain of

i) relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia **and**

iii) analgesia that is well sustained.

As previously discussed, Eriksen fails to teach formulations that have the desired combination of a) and b) with c). It teaches a) and b), but not c). It is thus not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides this combination of a), b) and c).

Even if Eriksen were used, it is not enough for Watts just to teach to adjust to achieve c) - maintenance of therapeutic plasma concentration levels, but that in doing so, the resultant formulation will have or retain a) and b) - relatively high maximum plasma concentrations at a relatively short time after nasal administration.

In the context of point 4. of *Graham v. John Deere*, the teaching of Watts must be read **as a whole** as it would be considered by one skilled in the art, and not with hindsight selectivity. It must also be taken into consideration that Watts also clearly teaches the following:

Watts teaches that its formulations may be used for local and systemic administration.

If for local administration, Watts teaches that the formulation **should not** enhance transmucosal absorption of a drug into systemic circulation, i.e. it **should not** give rise to any significant plasma concentration, still less at a short time after administration (p. 3, ll. 21 on). This is an essential part of the activity profile of the formulations of Eriksen, and Watts teaches directly away from it.

If for systemic administration, Watts teaches that its compositions are used to control the plasma concentrations of drugs, in particular to retard the transmucosal absorption of drugs which are readily absorbed, and where peak plasma concentrations are to be avoided (p.14, ll. 12

on). This is an essential part of the activity profile of the formulations of Eriksen, and Watts teaches directly away from it.

Again, the thrust of the examples of Watts relate entirely to formulations which **do not** enhance transmucosal absorption of a drug.

In all aspects it teaches directly away from rapid high initial plasma levels, i.e. directly away from the formulations of Eriksen.

Thus, even if Eriksen were used as a basis, Watts teaches that its formulations will desirably impair the rapid high plasma levels of Eriksen. Watts is thus not a document that would be combined with Eriksen by one skilled in the art in the reasonable expectation of providing formulations with

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained.

The combination of Eriksen viso Watts thus cannot render these claims obvious.

The §103 rejection of claims 2 - 15, 38, 39, 41 has been made over Eriksen as the primary citation viso Reich and Nairn. These rejections stand or fall with claim 1, so no further comment is made here.

Claims 16 and 53 - 59

A §103 rejection of claims 16 and 53 to 59, etc has been made over Eriksen as the primary citation viso Koochaki.

Eriksen is concerned with buprenorphine spray solutions for nasal administration. In relation to Koochaki, this document is concerned with the provision of a sustained release pharmaceutical composition. As discussed in the "Background of the Invention" section in Koochaki, "[v]arious pharmaceutical preparations for application to the nasal cavity such as nasal ointments, jellies, nose drops and sprays are known in the art ... [n]ose drops and sprays have the disadvantage, moreover, that it is difficult to retain the active drugs contained therein for an extended period of time" (page 2, lines 10 to 15). The solution proposed by Koochaki is to provide the composition in powder form comprising a drug, a nonionic cellulose ether derivative and a chitin-derived polymer. This is said to solve the common problem of "roll-back" commonly associated with spray and drop formulations. Thus, Koochaki recognises that

there are problems associated with spray and drop formulation and provides a solution in which the pharmaceutical is presented in the form of a powder.

If the skilled person was to consider adapting the formulations of Eriksen based on the teaching of Koochaki, the major change that he would make would be to make the pharmaceutaical in powder form. Based on a combination of these documents, he would not be able to derive the subject matter of the present claims in which the pharmaceutical is an aqueous solution.

The Examiner has referred to page 2, line 16 to 22 of Koochaki and considers that this passage teaches that the gelling agents could be used in a solution that gels upon introduction to the nasal cavity. However, this passage is a description of the prior art and has no bearing upon the teaching of Koochaki. There is no indication in Koochaki that the powder formulations of this document would be in any way effective if presented in solution form. In fact the teaching of Koochaki is entirely at odds with this since Koochaki teaches that the powder formulations solve the problems associated with drops and sprays. There is no indication in Koochaki that would lead to the skilled person to formulations that were in any form other than powder. The present claims are therefore not obvious from Eriksen and Koochaki.

In addition, Eriksen's formulations differ from the present buprenorphine - formulation as follows:

a) the absence of chitosan and hydroxypropylmethylcellulose,

b) a pH of about 7, and not 3 - 4.8.

Koochaki's formulations differ from the present buprenorphine formulation as follows:

i) they are solid powder formulations, and not aqueous solutions, and

ii) to achieve this solid powder form, they have to contain very high percentages by weight of chitosan and hydroxypropylmethylcellulose, typically of the order of 87% (see its examples),

iii) they contain no buprenorphine as such.

The levels of chitosan and hydroxpropylmethyl cellulose in the present liquid formulations with the desired activity profile are 0.0002 to 0.035% (0.2 to 35 mg/ml = mg/g of aqueous solution). In contrast, Koochaki's formulations contain percentages by weight of

chitosan and hydroxypropylmethylcellulose that are some 2,500 to 450,000 times greater than in the present compositions.

The very low percentages by weight of chitosan and hydroxypropylmethylcellulose in the present liquid formulations (0.0002 to 0.035% (0.2 to 35 mg/ml = mg/g of aqueous solution)) are **essential** to the activity profile of the present liquid and/or gel formulations, the desired activity profile being:

a) high maximum drug plasma concentrations,

b) at a relatively short time after administration, **and**

c) for the maximum plasma concentration to be well sustained.

For the reasons set out for claims 48 to 50 above, Eriksen is not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides the combination of

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained,

Even if Eriksen were used, it is not enough for Koochaki just to teach to adjust to achieve c) - maintenance of therapeutic plasma concentration levels, but that in doing so, the resultant formulation will have or retain a) and b) - relatively high maximum plasma concentrations at a relatively short time after nasal administration.

Koochaki nowhere teaches to adjust the formulations of Eriksen in the expectation of providing a nasal buprenorphine composition with the desired activity profile.

The thrust of Koochaki is towards the solving the problem that it perceives with jelly and spray formulations for delivering drugs in the nasal cavity, viz the lack of sustained presence of the drug on the nasal mucosa (as symptomised by 'roll-back'), and the consequent lack of sustained release.

Furthermore, from the passage at page 3, lines 35 – 52, it can be seen that Koochaki is mainly concerned with delivering drugs in the nasal cavity which are for the local/topical treatment of nasal diseases, where it is necessary for such local/topical treatment to have a sustained presence of the drug on the nasal mucosa. Prolonged retention *in situ* merely potentially enhances sustained local levels of the medicament. It has absolutely nothing to do

per se with enhancing rapid uptake and high initial systemic levels. Koochaki thus nowhere teaches anything about formulations which promote the transmucosal absorption of buprenorphine to give rapid high levels of the drug **systemically.**

The examiner is incorrect in his assertion (item 33) that Koochaki teaches to incorporate chitosan and hydroxypropylmethylcellulose into liquid buprenorphine compositions to arrive at the present liquid formulations. For the latter to be sprayable, these must form only 0.0002 to 0.035% (0.2 to 35 mg/ml = mg/g) of the aqueous solution.

Koochaki teaches that the only solution to the problem of ensuring a sustained presence of the drug on the nasal mucosa for the local/topical treatment of nasal diseases is to avoid any liquid and/or gel compositions and methods of treatment entirely, and to use such heavy loadings of chitosan and hydroxypropylmethyl- cellulose (that are some 2,500 to 450,000 times greater than in the present compositions) that they produce solid powder formulations. Such formulations are not said to be sprayable, and indeed Koochaki is entirely silent as to their mode of application.

That is, Koochaki provides no incentive towards the present liquid formulations with the desired activity profile. The combination of Eriksen viso Koochaki thus cannot render claim 16 obvious.

Claims 19, 60 - 66

The §103 rejection of claim 19 has been made over Eriksen as the primary citation viso Williams.

The formulations of the present invention provide

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained.

Eriksen provides buprenorphine solutions for nasal administration in which the drug is quickly absorbed into the system. Williams is concerned with compositions that provide long-lasting local anasthesia with low systematic absorption (page 2, lines 10 to 18). Based on this, the skilled person would not consider Williams to be a suitable document for the provision of a formulation which provided a relatively high maximum plasma concentration. Thus the skilled person would not consider the combination of Williams and Eriksen when faced with the

problem of the present invention. In addition, there is no direction within Williams which would lead to the combination of a chitosan and a polyox. These substances appear within a long list in this document. However, there is no indication that they should be combined and no indication that a combination of these components can lead to formulations which provide

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained.

The subject matter of the present claims is therefore not obvious from a combination of these documents.

In addition, the formulations of Eriksen differ from the present buprenorphine - chitosan - polyox formulation as follows:

i) the absence of chitosan and a polyox, and

ii) a pH of about 7, and not 3 - 4.8.

For the reasons set out for claims 48 to 50 above, Eriksen is not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition for **systemic** action with

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained,

resulting in the major advantage when used in the treatment of pain of

i) relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia **and**

iii) analgesia that is well sustained.

Even if Eriksen were used as a basis for this quest, Williams nowhere teaches to adjust the formulations of Eriksen in the expectation of providing a nasal buprenorphine composition with the desired activity profile **systemically**.

Again, Williams must be read as a whole, and not have passages selected out of it with hindsight. There is no unambiguous teaching in Williams of specific formulations which comprise the combination of a chitosan and a polyox, or of a chitosan - polyox composition with the desired activity profile. Claim 6 and the thrust of the passages cited by the Examiner are to

mucoadhesives that are polyox block copolymers; there is no clear teaching of a mucoadhesive that is a combination of chitosan and a polyox. If Williams teaches the skilled person anything, it is to incorporate polyox alone into the formulations of Erikson, not the specific combination of chitosan and polyox.

Even if that were not the case, the thrust of Williams is entirely towards formulations for delivering drugs to mucosa (e.g. nasal mucosa) for long-lasting local anaesthesia. Prolonged retention *in situ* merely potentially enhances sustained local levels of the medicament. It has absolutely nothing to do *per se* with enhancing rapid uptake and high initial systemic levels. Moreover, Williams teaches local anaesthesia, *i.e.* a lack of or at most negligible transmucosal absorption of anaesthetic and consequently no or a negligible systemic plasma concentration.

Williams clearly teaches directly away from formulations with

a) relatively high maximum systemic plasma concentrations,

b) at a relatively short time after administration, and

c) sustained plasma levels.

Thus, even if Eriksen were used as a basis for his quest, Williams is not a document that would be considered by one skilled in the art seeking to adjust the formulations of Eriksen. The combination of Eriksen viso Williams thus cannot render claim 19 obvious.

Since the examiner has made the double patenting rejection of various claims in sections 40 - 55 of the action provisional over the copending '315 citation, applicants suggest that these points should be held in abeyance until the scope of the relevant '315 claims are clearer.

The examiner has also made a **non-provisional** obviousness double patenting rejections of various claims in sections 56 - 60 of the action over US 6 387 917 (Illum). These are incorrect. The thrust of Illum is entirely to compositions for parenteral or non-parenteral administration of a systemically acting opioid analgesic in which the solubilising methanesulphonate anion enhances absorption of a drug. In particular, its examples are entirely towards the use of that salt of morphine.

There is no teaching whatsoever in Illum of formulations for the nasal cavity that comprise buprenorphine or a salt thereof. The gap between Illum and the present invention that must be filled in order to render the present invention obvious is a teaching in Illum or another

document to select buprenorphine from the general opioids and to provide nasal compositions of it or its salts. There is no such teaching in Illum.

There must also be an incentive to make that change in the reasonable expectation of success of providing a formulation which will give

i) a relatively high maximum plasma concentration at a relatively short time after administration, **as well as**

ii) relatively well sustained plasma levels.

There is no such incentive.

Illum is thus not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides the major advantage of

i) relatively rapid onset of analgesia after administration,

ii) a close to optimum level of analgesia and

iii) analgesia that is well sustained,

in the reasonable expectation of success

Illum thus does not render the relevant present claims obvious.

Additional Points

In light of 37 CFR §1.78(f)(1), attention is directed to co-pending US application no. 11/798,384 which is listed in its published version on the attached PTO/SB/08A. .

Summary

It is submitted that this application is in order for allowance. Favorable reconsideration of the application is requested.

Respectfully submitted,

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